RESEARCH

FULL ACCESS

3D WRITING OF MULTICELLULAR TENDON-ON-CNC-CHIP MODELS

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Abstract

Relevant *in vitro* models emulating tendinopathies are highly needed to study these diseases and develop better treatments. We have recently proposed a new strategy that allows the automated 3D writing of microphysiological systems (MPS) embedded into its own biomimetic fibrillar support platform based on the self-assembling of cellulose nanocrystals (CNCs). Here, we explored this CNC platform for writing humanized *in vitro* tendon models using tendon decellularized extracellular matrix (dECM)-based bioinks to closely recapitulate the biophysical and biochemical cues of tendon cell niche and self-induce the tenogenic differentiation of stem cells. The proposed concept was further explored to study the crosstalk between the tendon core and vascular compartment.

Porcine flexor tendons were decellularized to produce the dECM bioink hydrogel. hASCs were used as cell source and the bioink was directly printed within the CNC fluid gel. Tendon constructs were co-printed with compartmentalized microvascular structures to evaluate the cellular crosstalk with endothelial cells. The tendon-on-chip models showed high cell viability and proliferation during culture up to 21 days, and the synergy between dECM cues and printed patterns induced anisotropic cell organization similar to tendon tissues. Gene and protein analysis showed upregulation of the most important tendon related markers on tendon constructs, demonstrating that the biophysical and biochemical cues of dECM induced hASCs commitment toward tenogenic phenotype. In co-culture system, chemotaxis induced endothelial cells migration toward the tendon compartment, but without significant infiltration. Gene and protein expression results suggest that the cellular crosstalk established in this MPS with endothelial cells boosted hASCs tenogenesis, emulating tendon development stages.

Overall, the proposed system might be promising for the automated fabrication of organotypic tendon-on-chip models that will be a valuable new tool to study tendon physiology, pathology, or the effect of drugs for the treatment of tendinopathy.

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